Morning Cortisol Levels and Cognitive Abilities in People With Type 2 Diabetes The Edinburgh Type 2 Diabetes Study

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OBJECTIVE — People with type 2 diabetes are at increased risk of cognitive impairment but the mechanism is uncertain. Elevated glucocorticoid levels in rodents and humans are associated with cognitive impairment. We aimed to determine whether fasting cortisol levels are associated with cognitive ability and estimated lifetime cognitive change in an elderly population with type 2 diabetes.

RESEARCH DESIGN AND METHODS — This was a cross-sectional study of 1,066 men and women aged 60–75 years with type 2 diabetes, living in Lothian, Scotland (the Edinburgh Type 2 Diabetes Study). Cognitive abilities in memory, nonverbal reasoning, information processing speed, executive function, and mental flexibility were tested, and a general cognitive ability factor, *g*, was derived. Prior intelligence was estimated from vocabulary testing, and adjustment for scores on this test was used to estimate lifetime cognitive change. Relationships between fasting morning plasma cortisol levels and cognitive ability and estimated cognitive change were tested. Models were adjusted for potential confounding and/or mediating variables including metabolic and cardiovascular variables.

RESULTS — In age-adjusted analyses, higher fasting cortisol levels were not associated with current *g* or with performance in individual cognitive domains. However, higher fasting cortisol levels were associated with greater estimated cognitive decline in *g* and in tests of working memory and processing speed, independent of mood, education, metabolic variables, and cardiovascular disease ($P < 0.05$).

CONCLUSIONS — High morning cortisol levels in elderly people with type 2 diabetes are associated with estimated age-related cognitive change. Strategies targeted at lowering cortisol action may be useful in ameliorating cognitive decline in individuals with type 2 diabetes.

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Type 2 diabetes is associated with cognitive impairments, including deficits in processing speed, executive function and declarative memory, and with structural changes in the brain including reductions in hippocampal and amygdalar volumes, which are key areas influencing learning and long-term memory (1,2). Hyperglycemia, cerebral microvascular disease, and recurrent severe hypoglycemic episodes have all been implicated as potential causative factors of cognitive decline (3) but are unlikely to explain the entire effect of diabetes on cognition.

Increasing evidence supports a link between elevated plasma glucocorticoids and cognitive dysfunction. Exogenous glucocorticoid administration and elevated endogenous glucocorticoids (as occurs in Cushing's syndrome) are associated with cognitive impairment in animals and humans. More subtle alterations in hypothalamic-pituitary-adrenal (HPA) axis function have also been linked with cognitive function, with higher plasma cortisol levels at 0900 h being associated with poorer age-related cognitive ability in a small group of elderly, healthy male volunteers (4). Conversely, manipulations that reduce plasma glucocorticoid concentrations or their effects on target tissues can attenuate cognitive decline with ageing in rodents (5,6). Elevated glucocorticoid levels have widespread effects within the central nervous system, including deleterious effects on the structure and function of the hippocampus, a key locus for cognitive function, which also highly expresses glucocorticoid receptors (7,8).

Several studies have demonstrated that people with type 2 diabetes have activation of the HPA axis, manifested by elevated basal plasma cortisol levels (9,10), higher late-night salivary cortisol levels (11), elevated ACTH levels (12), increased cortisol levels following overnight dexamethasone suppression (13,14), and impaired habituation of cortisol levels to repeated stress (15). These findings are consistent with a central dysregulation of the HPA axis in type 2 diabetes. The elevated plasma cortisol levels are associated with metabolic abnormalities in diabetes (16) and with complications of diabetes, including retinopathy, neuropathy, and nephropathy (17).

Investigators have started to explore whether altered HPA axis activity contributes to cognitive impairment in diabetes. Impaired central negative feedback control of the HPA axis, as indicated by

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higher cortisol levels after 1.5 mg dexamethasone administration, was related to declarative memory impairments, possibly reflecting hippocampal dysfunction, in 30 individuals with type 2 diabetes compared with age-, sex-, and education-matched control subjects (18). However, the association between cortisol and cognitive function disappeared after adjustment for glycemic control (A1C). The same investigators reported similarly impaired HPA axis feedback control in association with verbal declarative memory deficits in 41 subjects with type 2 diabetes (1). In the latter study, the subjects with type 2 diabetes also had reduced hippocampal and prefrontal volumes, but there were no significant associations between the cortisol measurements and magnetic resonance image findings (1).

Despite these findings from animal and human studies, information from large-scale epidemiological studies of representative populations is lacking, which could confirm or refute an association between circulating plasma cortisol levels and age-related cognitive impairment. We therefore examined the relationship between fasting cortisol and both late-life cognitive ability and estimated lifetime cognitive change in a large, representative study population of people with type 2 diabetes (the Edinburgh Type 2 Diabetes Study [ET2DS]). The ET2DS has the advantage over many previous epidemiological studies of having detailed cognitive testing in a range of cognitive domains and very extensive phenotyping for potential confounding or mediating factors.

RESEARCH DESIGN AND METHODS

This report on the study cohort is based upon the cross-sectional phase of the ET2DS, an epidemiological study investigating mechanisms and risk factors for diabetes-related cognitive decline and for the development and progression of micro- and macrovascular disease in diabetes (19). Participants in the ET2DS, aged 60–75 years, were recruited at random from a comprehensive database of all subjects with established type 2 diabetes, living in the Lothian area of central Scotland between August 2006 and August 2007. Recruitment and examination of the study cohort has been described in detail previously (19). Ethical approval was obtained from the local research ethics committee, and all subjects gave written, informed consent. Subjects taking glucocorticoid therapy by any route within the last 3 months ($n = 147$) were also excluded from the current analysis, leaving a sample size of 919.

Clinical protocol

Briefly, subjects attended a local research clinic after an overnight fast. A fasting venous blood sample was taken between 0800 h and 0830 h, for measurement of cortisol and other biochemical parameters. Subjects completed questionnaires describing baseline demographics and underwent detailed physical examination and cognitive testing.

Subjects completed a self-administered questionnaire, including validated questions on education (highest level attained); a medical diagnosis of myocardial infarction, stroke, or angina; duration of diabetes; smoking; frequency of alcohol consumption over the last year; and the World Health Organization chest pain questionnaire. Height, weight, brachial blood pressure, and posterior tibial and dorsalis pedis systolic pressures (for calculation of the ankle-brachial index [ABI]) were measured and an electrocardiogram was (ECG) recorded. Data were collected from the information and statistics division of the National Health Service Scotland on all medical and surgical discharges from Scottish hospitals since 1981 (SMR01 scheme). Any ICD-10 or ICD-9 codes for cardiovascular or cerebrovascular disease were extracted and used together with self-reported vascular disease and findings from the chest pain questionnaire and ECG (in addition to a review of clinical notes where required) to define myocardial infarction, angina, and stroke, according to predefined criteria.

Cognitive assessment

Cognitive ability was assessed on the same morning as the blood sampling and physical examination, after subjects had eaten a snack and blood glucose was confirmed as >4 mmol/l, using a battery of psychometric tests, providing a comprehensive and validated assessment of cognitive function and mood state (19). These included tests of nonverbal memory and immediate and delayed verbal memory (faces and family pictures subtest [FACES]), logical memory (LM) (from the Wechsler Memory Scale III U.K.), working memory, nonverbal reasoning, processing speed (letter-number sequencing [LNS]), matrix reasoning (MR), digit symbol test (DST) (from the WAIS III U.K.), executive function (verbal fluency test [VFT]), and mental flexibility (trail-making test, part B [TMT]). A test of vocabulary (typically used to assess "crystallized" intelligence) was also included, using the combined Junior and Senior Mill Hill Vocabulary Scale (MHVS) synonyms (19). As results on vocabulary tests such as the MHVS vary little with aging, they are used to approximate peak prior cognitive ability. Subjects were also assessed using the Hospital Anxiety and Depression Scale (HADS), since mood can affect cognitive test results.

Laboratory analysis

Plasma cortisol levels were measured by radioimmunoassay (MP Biomedicals, Cambridge, U.K.) with intra-assay coefficient of variation (CV) 5.1–7.0% and interassay CV 6.0–7.9%.

Statistical analysis

Data were analyzed using SPSS version 15.0. As the distribution of TMT scores was skewed, we used natural log to transform TMT scores (lnTMT). Scores from the seven cognitive tests were used to test for the presence of a general cognitive ability factor, *g*, via a principal-components analysis. Scree slope analysis indicated that there was only a single principal component, which accounted for 44.0% of the total test variance. Each individual test loaded strongly on the first unrotated principal component (*g*; range 0.454–0.794); only the loading for the TMT was negative (−0.794) due to a high score on this test reflecting lower cognitive ability.

To examine associations between cortisol levels and current cognitive ability, linear regression was used to assess the association between cortisol and unadjusted cognitive test scores and then age- and sex-adjusted cognitive test scores. To examine associations between cortisol levels and estimated lifetime cognitive change, linear regression was used with additional adjustment for MHVS. A further model also included adjustment for additional covariates to control for mood (HADS score), duration of diabetes and glycemic control (A1C), cardiovascular risk factors (total cholesterol, BMI, hypertension, smoking, and alcohol intake), cardiovascular disease (myocardial infarction, angina, stroke, ABI), and level of education. Finally, we tested all the interaction terms between cortisol and all the variables included in the regression analysis. Significant interaction terms were entered into a further regression model.

RESULTS

Subject characteristics and potential confounding factors

Characteristics of the study population are shown in Table 1. Characteristics of the 919 subjects who were recruited into the ET2DS were similar to those of nonresponders in terms of age, multiple deprivation category, duration of diabetes, A1C levels, the proportion using insulin, total cholesterol, and systolic blood pressure (data not shown). Table 2 shows the correlations between cortisol and cognitive and metabolic variables. Cortisol levels were similar in men and women. Cortisol levels increased slightly with age but did not differ according to smoking or alcohol consumption, marital status, or education. All tests of cognitive function were poorer with increasing age and those with higher HADS depression scores.

Cortisol and cognitive ability

In univariate analyses, cortisol was not associated with current general cognitive ability (*g*) or with individual tests of cognitive function (Table 3). Trends for an association of higher cortisol levels with poorer working memory and processing speed (assessed by LNS and DST) were absent after adjustment for age and sex (Table 3, *model 1*). Cortisol was not associated with peak prior cognitive ability measured by MHVS.

After adjustment for MHVS to estimate cognitive change from an individual's estimated prior function and age and sex, higher cortisol levels were associated with poorer working memory (LNS) and processing speed (DST) ($P < 0.05$) (Table 3, *model 2*). These associations persisted ($P < 0.05$) after inclusion of other potential confounding factors in the model (Table 3, *model 3*).

Finally, we tested for interaction terms between cortisol and all the variables included in the regression analysis (Table 3, *model 4*). There were no significant interaction terms for any of the cognitive domains other than for LNS and *g*. In the regression analysis for LNS, two interaction terms entered the equation, namely cortisol by ABI and cortisol by alcohol. Inclusion of these interaction terms modestly altered β, but the model remained significant. In the regression analysis for *g*, there was also an interaction between cortisol and ABI. Inclusion of this interaction term resulted in the final model achieving statistical significance. Results of this model are illustrated

Table 1—*Characteristics of study participants in ET2DS*

	All subjects
n	919
Sociodemographic and lifestyle variables	
Age at assessment (years)	67.9 (4.2)
Marital status	
Married	649 (70.8)
Living with long-term partner	49 (5.3)
Single	131 (14.3)
Widowed	88 (9.6)
Education	
University/college	148 (16.1)
Other professional qualification	265 (28.8)
Secondary school	500 (54.4)
Primary school	6 (0.7)
Current smoking	120 (13.1)
Alcohol consumption (frequency)	
Never	187 (20.5)
One to four times/month	402 (44.0)
Two to five times/week	229 (25.1)
Six or more times/week	96 (10.5)
Cognitive assessment	
Mini-Mental State Examination	28.3 (1.9)
MHVS	31.0 (5.2)
Faces and family pictures subtest	65.9 (7.9)
Logical memory	25.2 (8.2)
LNS	9.7 (2.7)
Matrix reasoning	13.0 (5.3)
DST	49.5 (14.9)
Verbal fluency test	36.9 (12.8)
lnTMT	4.68 (0.4)
General cognitive ability factor (*g*)	0.01 (0.99)
Anxiety and depressive symptoms	
HADS anxiety score	5.6 (3.9)
HADS depression score	3.8 ± 2.8
Plasma cortisol levels (nmol/l)	733 (192)
Diabetes and metabolic variables	
Duration of diabetes (years)	9.1 (6.5)
Systolic blood pressure (mmHg)	133.2 (16.3)
Diastolic blood pressure (mmHg)	69.1 (9.1)
Total cholesterol (mmol/l)	4.3 (0.9)
A1C (%)	7.4 (1.1)
BMI (kg/m^2)	31.3 (5.6)
Ischemic heart disease (angina or myocardial infarction)	278 (30.3)
Myocardial infarction	126 (13.7)
Angina	252 (27.4)
ABI*	0.98 (0.21)
Cerebrovascular disease (transient ischemic attack or stroke)	81 (8.8)
Treatments	
Treatment of diabetes	
Diet alone	171 (18.6)
Hypoglycemic oral agents	590 (64.2)
Insulin with or without hypoglycemic oral agents	158 (17.2)
Lipid-lowering drugs	777 (84.5)
Antihypertensive treatment	725 (78.9)
Antidepressant(s)	108 (11.8)

Data are means ± SD or *n* (%). *ABI, lowest ankle systolic pressure divided by higher of two brachial systolic pressures, a measure of subclinical atherosclerosis.

Table 2—*Correlations between clinical variables, plasma cortisol, and cognition*

	Cortisol	MR	LNS	VFT	DST	lnTMT	FACES	LM	*g*
Demographic variables									
Age	0.066*	−0.171†	−0.151†	−0.074*	−0.202†	0.185†	−0.136†	−0.100‡	−0.225†
Female sex	0.003	−0.137†	−0.035	−0.009	0.181†	−0.053	0.191†	0.111‡	0.059
Current smoking	−0.021	−0.023	0.081*	0.054	−0.035	0.015	−0.034	0.026	0.014
Alcohol intake (drinks/week)	0.037	0.172†	0.145†	0.145†	0.038	−0.028	0.029	0.052	0.134†
Anxiety and depressive symptoms									
HADS anxiety	0.010	−0.146†	−0.137†	−0.131†	−0.083*	0.121†	−0.018	−0.056	−0.147†
HADS depression	0.044	−0.154†	−0.131†	−0.119†	−0.187†	0.179†	−0.066*	−0.107‡	−0.208†
Diabetes and metabolic variables									
Duration of diabetes (years)	0.036	−0.008	−0.071*	−0.069*	−0.140†	0.112‡	−0.109‡	−0.033	−0.111‡
Systolic blood pressure (mmHg)	0.047	−0.019	−0.041	−0.040	−0.011	0.049	0.026	−0.009	−0.039
Diastolic blood pressure (mmHg)	0.005	0.073*	0.037	0.016	0.027	0.001	0.032	−0.043	0.032
Total cholesterol (mmol/l)	0.152†	0.018	0.047	0.022	0.056	−0.019	0.048	−0.012	0.051
A1C (%)	0.034	0.005	−0.033	−0.066*	−0.038	0.005	−0.021	−0.012	−0.029
BMI	−0.088‡	−0.053	0.007	−0.054	−0.028	0.001	0.016	0.029	0.034
Myocardial infarction	−0.009	−0.060	−0.039	−0.026	−0.146†	0.086*	−0.111‡	−0.030	−0.118†
Angina	0.027	−0.096‡	−0.066*	−0.014	−0.157†	0.099‡	−0.081*	−0.060	−0.141†
ABI	−0.048	−0.064	0.021	0.010	0.075*	−0.026	0.0	0.022	−0.049
Cerebrovascular disease	0.011	−0.060	−0.082*	−0.062	−0.135†	0.110*	−0.066*	−0.067*	−0.142†

*$P < 0.05$; †$P < 0.001$; ‡$P < 0.01$.

in Fig. 1 and in online appendix Table 1 (available at http://care.diabetesjournals.org/cgi/content/full/dc09-1796/DC1).

CONCLUSIONS — Evidence from both animal and human studies supports the premise that high cortisol levels have an adverse effect on cognitive decline, but only a few small studies have suggested that this may occur in people with diabetes (1,18). In this large study of elderly men and women with type 2 diabetes, we found that higher fasting morning cortisol levels were not related to current cognitive ability but were associated with estimated cognitive change, that is, with some tests of current cognitive functioning after adjustment for estimated prior cognitive ability. Specifically, higher cortisol levels were associated with significantly lower general cognitive ability (*g*) and with significantly poorer scores on LNS (working memory) and DST (processing speed) and with trends for poorer cognitive function in other domains, including mental flexibility, nonverbal memory, immediate and delayed memory, and general cognitive ability.

We found significant associations of higher cortisol levels with two cognitive domains, including working memory and poorer processing speed. The latter is the first cognitive domain to show a decline with ageing, shows large declines, and is an early predictor of dementia (20). The smaller published studies in the literature have reported only an association between cortisol and verbal declarative memory in younger subjects with diabetes (aged <60 years) (1,18). Our subjects were older, which may explain the different findings. In addition, as our subjects were extensively phenotyped, it was possible to adjust for several potential confounding factors influencing cognitive performance. Indeed, the relationships between cortisol and estimated cognitive change were independent of current met-

Table 3—*Multivariate associations between cortisol and late-life cognition and estimated cognitive change**

	Unadjusted		Model 1 +Sex and age		Model 2 +MHVS		Model 3 +Other covariates†		Model 4 +Interactions‡	
	β§	*P*	β	*P*	β	*P*	β	*P*	β	*P*
MR	−0.04	0.28	−0.03	0.46	−0.04	0.18	−0.05	0.08	NSI	
LNS	−0.06	0.07	−0.05	0.13	−0.07	0.04	−0.07	0.02	−0.44	0.002
VFT	0.04	0.27	0.04	0.21	0.03	0.36	0.02	0.51	NSI	
DST	−0.06	0.07	−0.05	0.13	−0.07	0.03	−0.06	0.04	NSI	
lnTMT	0.05	0.13	0.04	0.24	0.05	0.09	0.05	0.12	NSI	
FACES	−0.05	0.13	−0.05	0.08	−0.06	0.09	−0.06	0.07	NSI	
LM	0.04	0.20	0.05	0.16	0.04	0.27	0.05	0.13	NSI	
g	−0.05	0.20	−0.03	0.37	−0.05	0.09	−0.05	0.06	−0.30	0.015

*Cognitive test scores adjusted for MHVS. †Other covariates = HADS score, duration of diabetes, A1C, total cholesterol, BMI, hypertension, smoking, alcohol intake, myocardial infarction, angina, stroke, ABI, and level of education. ‡Interactions between plasma cortisol and covariates were tested for all models. Significant interactions were included in the LNS model (cortisol by ABI: $\beta = 0.572$, $P = 0.002$; cortisol by alcohol intake: $\beta = -0.436$, $P = 0.001$) and the *g* model (cortisol by ABI: $\beta = 0.331$, $P = 0.038$). §Standardized β. NSI, no significant interactions.

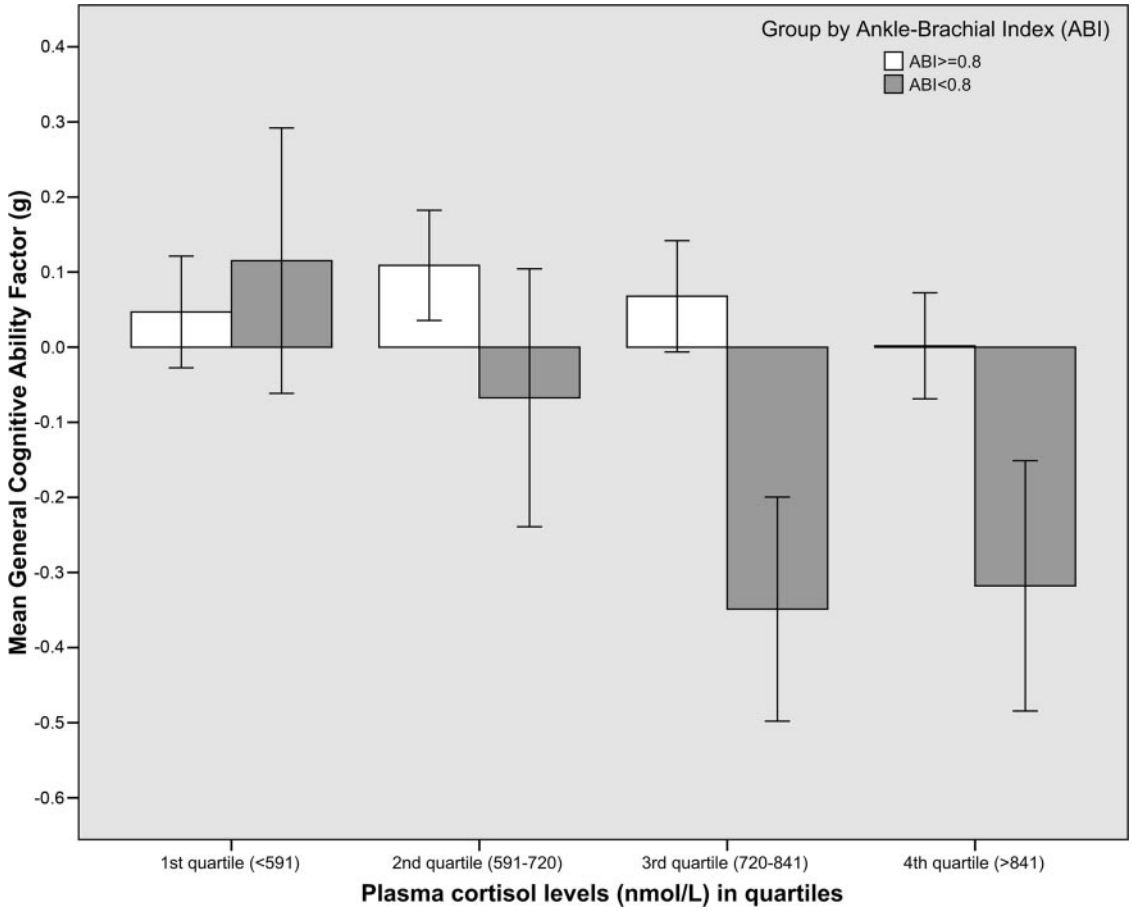

Figure 1—*Association between general cognitive ability factor (*g*) and fasting cortisol levels in quartiles. Significant decline in general cognitive ability, g, in association with higher fasting cortisol levels, particularly among those with subclinical atherosclerosis, as indicated by a lower ABI score (<0.8) (*P *< 0.05 in multiple regression analysis model 4 after adjustment for sex, age, MHVS, other covariates, and interactions).*

abolic and cardiovascular status, suggesting that there may be a direct link between cortisol and the brain. Mechanistically, the hippocampus is highly vulnerable to both age-related and metabolic insults and is particularly susceptible to the damaging effects of elevated cortisol. Glucocorticoids exert direct effects on hippocampal neurons, inhibiting long-term synaptic potentiation (the process thought to play a role in memory and learning) and also causing neuronal damage and reducing de novo neurogenesis (21). Glucocorticoids also have indirect effects, sensitizing neurons to metabolic and neurochemical challenges such as glutamate excess, oxidative stress, and disrupted calcium homeostasis. However, the direction of causality remains unknown as prospective studies of cognitive function in subjects without diabetes have suggested that hippocampal dysfunction potentially causes elevated cortisol levels (22).

The blood samples in our study were collected under carefully timed conditions in the morning, with all of the subjects in the fasting state. These fasting cortisol levels in our subjects were high (mean 730 nmol/l), but high fasting cortisol levels, associated with cognitive decline, were also reported in the much smaller published studies (1,18). The mechanisms underlying the high cortisol levels in diabetes are not known. Corticosteroid-binding globulin levels are not elevated in diabetes. Thus, these cortisol concentrations might reflect a stress response due to the combination of fasting, venesection, and the novel clinic setting in which the samples were obtained. However, we did not formally assess for current stress levels. It may be that people with diabetes are more susceptible to the effects of stress on plasma cortisol such that repeated cortisol elevations damage the hippocampus. Our own studies of impaired habituation of cortisol responses to venepuncture (15) would be consistent with activation of the HPA axis from higher centers in type 2 diabetes. Whether subjects with type 2 diabetes have impaired central negative feedback sensitivity of the HPA axis that contributes to high cortisol levels is not clear, with reports of both impaired (13,14) and enhanced (23) feedback responses. Further detailed studies including examining both the glucocorticoid and mineralocorticoid receptor components of central negative feedback sensitivity, as has recently been described in obesity (24), are required.

The strengths of this study include the large sample size and the application of a battery of seven psychometric tests, which provides a relatively comprehensive and validated assessment of cognitive domains and mood states. There was also detailed phenotyping for potential confounding or mediating factors. The study population had a verified clinical diagnosis of type 2 diabetes and was representative of the wider type 2 diabetic population (elderly, community-dwelling men and women with the full spectrum of severity of type 2 diabetes, from diet controlled to insulin treated). Many large-scale studies on people with diabetes are restricted to those attending hos-

pital clinics and biased toward the more severe end of the spectrum of diabetes. The main limitation of our study is its cross-sectional design. We accounted partly for this by adjusting for a vocabulary measure (MHVS), which allowed us to estimate lifetime cognitive change. In addition, the use of multiple statistical tests raises the possibility of our significant findings being type 1 errors. The tests we used are recognized to be sensitive and so we think this unlikely, but clearly the results need replicating in other populations.

If further investigation demonstrates that the relationship between cortisol and lifetime cognitive change is causal, such that higher lifetime levels of cortisol accelerate age-related cognitive impairment, it is possible that therapeutic manipulations that lower cortisol levels may help to improve cognitive function. Access of cortisol to the glucocorticoid receptor is regulated by local activity of the 11β-hydroxysteroid dehydrogenase enzymes (11β-HSDs), which catalyze the interconversion of the active steroid cortisol and its inactive metabolite cortisone. 11β-HSD1 reactivates cortisol from inactive cortisone in many central nervous system and metabolic sites, increasing activation of the glucocorticoid receptor. In a small, randomized, double-blind, placebo-controlled, crossover study, administration of the 11β-HSD inhibitor, carbenoxolone, improved verbal fluency after 4 weeks in 10 healthy elderly men (aged 55–75 years) and improved verbal memory after 6 weeks in 12 people with type 2 diabetes (25). Whether this short-term effect on cognitive ability could be reproduced over longer time periods, and therefore help reduce the cognitive decline associated with aging, is unknown. Notably, verbal fluency was not related to fasting plasma cortisol in the current study.

In conclusion, morning cortisol levels in elderly people with type 2 diabetes are high, with deleterious effects on cognitive function. Further investigation is required to determine the direction and nature of this relationship, which, if causal, would support the use of therapeutic strategies to lower cortisol action (25) to ameliorate cognitive decline in individuals with type 2 diabetes.

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